REMARKS

Claims 14-21 are all the claims pending in the application; each of the claims has been rejected.

I. Rejection of Claims Under 35 U.S.C. §103

At page 3 of the Office Action, claims 14-21 are rejected under 35 U.S.C. §103(a) as being obvious over Isomura et al. (USP 4,990,503), in view of Aparicio et al. (Leukemia 12:220-229 (1998)) and Shipman et al. (Br. J. Haematology 98:665-672 (1997)).

The Examiner states that Isomura et al. teaches that heterocyclic biphosphonic acid compounds useful as bone resorption inhibitors, including 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid[1] recited in the pending claims, can be used in medicinal compositions for oral administration, that the recited compound has a strong bone resorption inhibition activity which can be used in diseases such as metastatic osteocarcinoma, and that an oral dosage of the recited compound is between 0.1 and 10 mg per day.

The Examiner admits that Isomura et al. does not expressly teach that the recited compound is useful in a method of inhibiting proliferation of myeloma cells, or that the effective dosage of the compound is 1 to 20 mg or 3 to 10 mg.

The Examiner states that Aparicio et al. teaches two structurally different bisphosphonates: aredia (Pamidronate) and Zoledronate which are effective in suppressing bone resorption and in inducing apoptosis in multiple myeloma cells by inducing apoptotic

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[1] Also referred to a Compound A in the specification of the instant application.

fragmentation, and that both compounds are effective in inhibiting proliferation of multiple myeloma cells.

As to Shipman et al., the Examiner states that it teaches three structurally different bisphosphonates: Clodronate, Pamidronate and YM175 which are effective in reducing the cell number of human myeloma cells, and that the latter two compounds are effective in inducing DNA fragmentation in myeloma cells.

The Examiner concludes that it would have been obvious to the skilled artisan to use the recited compound, in the claimed dosage, in a method of inhibiting proliferation of myeloma cells and/or suppressing bone resorption. The Examiner explains that the motivation for doing so is because various structurally distinct bisphosphonate compounds (Zoledronate, Clodronate, Pamidronate and YM175) are known to be effective in inducing apoptosis in myeloma cells. Thus, according to the Examiner, the skilled artisan would reasonably expect that any known bisphosphonate compound, including the recited compound, could be used in the claimed method for inhibiting the proliferation of myeloma cells and/or suppressing bone resorption.

Applicants' Response

In response, Applicants assert that the presently claimed invention is not obvious over Isomura et al., in view of Aparicio et al. and Shipman et al., for the following reasons.

1. Regarding Isomura et al., as admitted by the Examiner this reference does not disclose compounds that inhibit proliferation of myeloma cells and that also suppresses bone resorption when administered to a patient suffering from multiple myeloma (MM), as recited in the pending claims.

As a matter of course, there is no disclosure in Isomura et al. whatsoever that compounds disclosed therein inhibit proliferation of myeloma cells when they are administered to MM patients. Thus, Isomura et al. provides no motivation to reach the present invention and the invention recited in the pending claims is not obvious over Isomura et al.

The Examiner states in the Office Action that "Isomura et al. also teaches the oral dosage of 1-hydroxy-2-(imidazo[1,2a]pyridin-3-yl)ethane-1,1-bisphosphonic acid to be useful in inhibiting bone resorption to be 0.1 to 10 mg daily." However, Applicants respectfully point out that the Examiner's understanding in this regard is incorrect. The dosage cited by the Examiner is for non-oral administration (see col. 7, lines 18-19) and the correct dose for oral administration is described to be "generally from 1 mg to 1 g (=1000 mg)/day/adult for oral administration" (column 7, lines 17-18). Applicants also note that this is an extremely broad range of potential dosages (1000 fold range) that may be used to inhibit bone resorption.

2. Regarding Aparicio et al., the Examiner points out that Aparicio et al. discloses the *in vitro* MM cell apoptosis-inducing activities of Pamidronate and Zoledronate. However, at page 226, column 2, lines 10-12, of this reference, it is described that "[w]hether or not MM targets are uniquely sensitive to the apoptotic, cytotoxic and/or cytostatic effects of bisphosphonates is unclear." Aparicio et al. continues by stating that "[a] more relevant question is whether these cytotoxic concentrations of Pamidronate or Zoledronate can be reached in treated patients. Certainly, peak serum concentrations are far below the required threshold but, owing to the singular skeletal distribution of administered bisphosphonates, marrow concentrations may be sufficient to inhibit growth of myeloma cells" (page 226, column 2, lines 32-38).

Thus, Aparicio et al. calls into question whether the concentration of Pamidronate or Zoledronate required to inhibit myeloma cell proliferation can even be reached in a patient when these bisphosphonates ("BPs") are administered orally. Also, Aparicio et al. neither discloses inhibition of myeloma cell proliferation by these BPs *in vivo* in MM patients, nor a certain basis for believing such would be successful.

3. Shipman et al. describes *in vitro* myeloma cell apoptosis activity in the presence of Clodronate, Pamidronate and YM175 (page 133, col. 2, to page 134, col. 2). Pamidronate is reported to have had apoptosis activity at 500 μM and YM175 had apoptosis activity at 100 μM. However, in this reference, these BPs were not administered *in vivo* to MM patients having bone lesions. Thus, this reference disclose neither inhibition of myeloma cell proliferation by these BPs *in vivo* in MM patients nor a certain basis for believing such would be successful.

4. Applicants state that the inhibition of myeloma cell proliferation in MM patients according to the present invention is not obvious over the *in vitro* myeloma cell apoptosis activity of the bisphosphonates reported in Aparicio et al. and Shipman et al. for the following additional reasons.

a. It is apparent that, in order to exhibit inhibition of myeloma cell proliferation in MM patients *in vivo*, at a minimum the concentration of the drug that exhibited apoptotic activity *in vitro* (such as in Aparicio et al. and Shipman et al.) should be achieved in the living body of the patient. The following article that was published after both Aparicio et al. and Shipman et al. discusses this point.

Beginning in the last paragraph of page 1703 of Dallas et al.[2], the results from experiments designed to test the influence of ibandronate on "*in vitro* growth and apoptosis of the 5TGM1 myeloma cell line" are discussed. The authors of this article take into account the report of apoptosis on myeloma cells *in vitro* published by Shipman et al. and Aparicio et al. (citations 10 and 11). Table 3 shows the results of the cytotoxic effects of ibandronate at 50 - 100 μmol. As stated in the middle of the first paragraph of page 1704, because the estimated peak serum concentration *in vivo* is 5 μmol/L, "[u]sing this dose range [5 μmol/L], no significant effect was seen with ibandronate or risedronate on the total number of myeloma cells...".

Taking into account the maximum concentration of the drug which is actually achieved in the living body of MM patients (5 μmol/L in the case of ibandronate), one skilled in the art would have believed that it would be difficult to achieve a sufficient concentration of the drug *in vivo* to result in sufficient apoptosis activity when the compound is required to be present in a concentration at least 10 fold higher to achieve a minimal level of *in vitro* activity (e.g., 50 μmol for ibandronate). The skilled artisan would not have believed that a high enough concentration of the compounds shown to have apoptotic activity *in vitro*, as disclosed in Aparicio et al. and Shipman et al., would be achieved to inhibit myeloma cell proliferation *in vivo* when administered to MM patients.

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[2] *Blood* 93:1697-1706 (1999), attached to the Response submitted in this application on August 22, 2002.

b. Neither Aparicio et al. nor Shipman et al. disclose results which teach or suggest that the effective *in vitro* concentration can also be achieved *in vivo* in MM patients.

c. Although many BPs have been subjected to clinical experiments, there is no clinical case wherein the clinical dose-achieving improvements of bone lesions could also be shown to produce a clear inhibition of MM cell proliferation *in vivo*.

Thus, while Aparicio et al. and Shipman et al. show inhibition of MM cell proliferation *in vitro*, neither teaches or suggests actual inhibition of MM cell proliferation in MM patients *in vivo*. Furthermore, the disclosure of Dallas et al. teaches away from the present invention in that based on the disclosure thereof, the skilled artisan would not expect that a high enough physiologically-effective concentration of a BP could be obtained *in vivo* to effectively treat a MM patient.

For these reasons, neither Isomura et al. alone, or in combination with Aparicio et al. and Shipman et al., make the present invention obvious.

5. Applicants also assert that the present invention would not have been obvious due to the unexpectedly superior effects of the compounds of the present invention, for the following reasons.

Example 4 of the present application (beginning on page 20) shows a clinical test result wherein Compound A (3 mg/day) according to the present invention is solely administered to MM patients *in vivo*. It was observed that the level of the M protein (IgD), which is a tumor marker, was clearly lowered in addition to a significant decrease of the bone resorption marker level. Thus, this Example clearly shows the fact that the Compound A according to the present

invention when administered to the MM patient with bone lesions, simultaneously inhibited myeloma cell proliferation and suppressed bone resorption.

It would not have been obvious to one skilled in the art that the specific activities of inhibition of myeloma cell proliferation and suppression of bone resorption, recited in the pending claims, could be exhibited in MM patient in the particular low dose range recited in claims, given the disclosures of Dallas et al discussed above, and the fact that no such *in vivo* results have been shown for any known BP.

The activity of Compound A of the present invention that simultaneously lowers a bone resorption marker and a tumor marker, in a dose that exhibits bone resorption suppressing activity with less side effects, has not been shown for the other BPs. Thus, such effects of Compound A are quite unexpected, and as there has been no *in vivo* evidence of a BP having the dual activities recited in the claims, the effects are unexpected superior over those of other BPs.

As explained above, even assuming that Isomura et al., which discloses bone resorption inhibition activity of Compound A, were combined with Aparicio et al. or Shipman et al., which disclose inhibition of MM cell proliferation *in vitro* by other BP, the method of both suppressing myeloma cell proliferation and suppressing bone resorption by administering Compound A to a patient exhibiting bone resorption accompanied by multiple myeloma (MM) is not obvious. Thus, the method of inhibiting both myeloma cell proliferation and bone resorption by administering Compound A to a MM patient is not obvious.

Compound A according to the present invention has an activity that has not been reported, i.e., both activities of inhibiting myeloma cell proliferation and suppressing bone

resorption in MM patients. Such excellent effects are unexpected from the references cited by the Examiner.

In conclusion, in view of these comments Applicants again assert that the presently claimed invention is not obvious over Isomura et al., in view of Aparicio et al. and Shipman et al., and therefore respectfully request reconsideration and withdrawal of this rejection.

II. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

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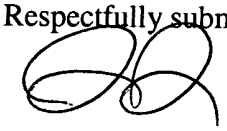
Respectfully submitted,



Drew Hissong
Registration No. 44,765

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860
WASHINGTON OFFICE

23373
PATENT TRADEMARK OFFICE

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